REMARKS

The Office Action mailed 15 December 2004 has been received and reviewed. Claims 78, 90, 91 and 95 having been amended, the pending claims are claims 1, 3-13, 21, 23, 24, 33, 36, 37, 41-47, 49-56, 59-69, 72, 73, 75-81 and 90-101.

Claims 1, 3-13, 21, 23, 24, 33, 36, 37, 41-47, 49-56, 59-68, 72, 73, 75-77, 92-94 and 96-101 have been allowed. Reconsideration and withdrawal of the rejection of claims 69, 78-81, 90, 91 and 95 is respectfully requested.

Rejection under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 78-81 and 95 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner alleged that claims 78 and 95 lack an active method step correlating the assay for EphA2 intracellular localization and phosphorylation with the determination of the disease stage of the cancer cells. This rejection is respectfully traversed. However, in order to advance prosecution of the above-identified patent application, claims 78 and 95 are amended to recite that the EphA2 intracellular localization pattern or EphA2 phosphorylation content that are detected in accordance with the claimed method are indicative of the disease stage of the cancer cells. It is respectfully submitted that the amendment obviates the rejection of claims 78-81 and 95 under 35 U.S.C. §112, second paragraph. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §101

The Examiner rejected claims 78-81 and 95 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Specifically, the Examiner alleges that in the absence of the recitation of an active method step, the claims read on a cognitive process for determining disease state. This rejection is respectfully traversed. However, it is submitted that the amendment to claims 78 and 95 as discussed above obviates the rejection of claims 78-81

and 95 under 35 U.S.C. §101 as well. The assay of EphA2 intracellular localization pattern and phosphorylation content as recited in amended claim 78 and 95 are linked with the determination of the disease stage. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §103(a)

The Examiner rejected claims 90 and 91 under 35 U.S.C. §103(a) as being unpatentable over Easty et al. (*International Journal of Cancer*, 1995;*60*:129-136) as evidenced by the abstract of Chen et al. (*Journal of Biological Chemistry*, 1998;*273*:24670-24675) and Lindberg et al. (*Molecular and Cellular Biology*, 1990;*10*:6316-6324) in view of Larrick et al. (In: Human Hybridomas and Monoclonal Antibodies, Englemen and Foung, Eds. 1985,8-9). In brief, the Examiner maintains that Easty et al. teach that elevated expression of Eck (EphA2) appeared to be correlated with metastasis to epithelial sites, as well as polyclonal antiserum specific for an intracellular domain of Eck, but do not teach detection of metastatic melanoma cells using a monoclonal anti-Eck antibody. Larrick et al. is cited as teaching the advantages of a monoclonal antibody over a polyclonal antibody. The Examiner concludes that it would have been *prima facie* obvious to one of skill in the art at the time the invention was made to make a monoclonal antibody that bind to amino acids 874-974 of Eck. This rejection is respectfully traversed.

Claim 90 has been amended to delete recitation of a change in EphA2 expression level. Claim 91, which is dependent therefrom, has been amended to affirmatively recite assaying for a change in EphA2 expression level since the antecedent basis for that step has been deleted from claim 90. Since none of the cited documents teach or suggest assaying a cell population for a change in EphA2 intracellular localization pattern or a change in EphA2 phosphorylation content as compared to the EphA2 intracellular localization pattern and phosphorylation content in an analogous normal cell population as recited in claim 90, as amended, it is respectfully submitted that the claims 90 and 91 are not rendered obvious by the cited documents. Reconsideration and withdrawal of the rejection of claims 90 and 91 under 35 U.S.C. §103(a) as being unpatentable over the cited references is respectfully requested.

The Examiner rejected claims 69, 90, and 91 under 35 U.S.C. §103(a) as being unpatentable over Easty et al. (International Journal of Cancer, 1995;*60*:129-136) and the abstract of Chen et al. (Journal of Biological Chemistry, 1998, 273: 24670-24675) and Lindberg et al. (Molecular and Cellular Biology, 1990;*10*:6316-6324) and Larrick et al. (In: Human Hybridomas and Monoclonal Antibodies, Engleman and Found, Eds. 1985:8-9) as applied to claims 90 and 91 above and in further view of Easty et al. (International Journal of Cancer 1997;*71*:1061-1065). This rejection is respectfully traversed.

Claim 69 is directed to a method for detecting the presence of metastatic cells in a cell population and recites, *inter alia*, incubating at least a portion of the cell population with a first antibody that specifically binds EphA2 to allow binding of the antibody to EphA2; detecting antibody-EphA2 binding; incubating the portion of the cell population with a second antibody having phosphotyrosine specificity; and observing the level of binding of the second antibody to cells in the cell population.

The Examiner maintains that Easty et al. (1997) teaches that in addition to Eck, other protein tyrosine kinases are ectopically expressed in melanoma and that it would be *prima facie* obvious to one of skill in the art at the time the invention was made to use an antibody which would specifically bind another protein tyrosine kinase that was known to be ectopically expressed, lost or over expressed in malignant melanoma. The Examiner goes on to state that the teachings of Easty et al (1997) indicate that the measurement of a single protein tyrosine kinase does not provide an absolute correlation with malignancy, and therefore one of skill in the art would be motivated to measure the expression of more than one tyrosine kinase.

The "first antibody" recited in claim 69 specifically binds EphA2, and the "second antibody" recited in claim 69 has "phosphotyrosine specificity." It appears that the Examiner may be confusing an antibody with "phosphotyrosine specificity" with an antibody that would specifically bind a particular tyrosine kinase. These are not the same. A phosphotyrosine specific antibody is not specific to any particular tyrosine kinase. It has a much lower level of specificity in that it binds phosphotyrosine moieties. For example, as noted at page 3, lines 26-

28, phosphotyrosine specific antibodies can be used to isolate tyrosine phosphorylated proteins (including EphA2) by affinity chromatography.

The motivation to evaluate the level of binding of a phosphotyrosine specific antibody to the cells arises from the observation that a diagnostic test that incorporates both an EphA2-specific antibody and a phosphotyrosine-specific antibody provides a sensitive test for distinguishing between normal, non-metastatic, and metastatic cells (see specification at page 8, lines 10-16). As further explained at page 5, lines 8-18 of the specification:

> Additionally, other antibodies may be used in combination with the antibodies of the present invention to provide further information concerning metastatic disease state. For example, the EphA2 of metastatic cells exhibits altered tyrosine phosphorylation. In normal breast epithelial cells, EphA2 is expressed and is tyrosine phosphorylated. However, in metastatic breast epithelial cells, EphA2 is overexpressed, and the EphA2 is not tyrosine phosphorylated. Because a test quantifying EphA2 expression sometimes may lead to an ambiguous result, it may be desirable to determine tyrosine phosphorylation, as well as the magnitude of EphA2 expression. Thus, a method of diagnosis using the antibodies of this invention in combination with phosphotyrosine-specific antibodies provides data for determining the state of metastatic disease.

Since none of the cited references teaches the use of a phosphotyrosine specific antibody, they fail to teach or suggest every element of the claim. Further, motivation to contact the cells with a phosphotyrosine specific antibody is absent in the art as none of the cited references teaches the significance of the phosphotyrosine content of EphA2 in distinguishing among normal, non-metastatic, and metastatic cells. It is respectfully submitted that the Examiner has for at least those reasons failed to make a *prima facie* case of obviousness. Reconsideration and withdrawal of the rejection of claims 69, 90 and 91 under 35 U.S.C. §103(a) as being unpatentable over the cited references is therefore respectfully requested.

Allowed Claims

The allowance of claims 1, 3-13, 21,23, 24, 33, 36, 37, 41-47, 49-56, 59-68, 72, 73, 75-77, 92-94 and 96-101 is acknowledged, with appreciation.

Summary

It is respectfully submitted that the pending claims 1, 3-13, 21, 23, 24, 33, 36, 37, 41-47, 49-56, 59-69, 72, 73, 75-81 and 90-101 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
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